BMS- 488043

Drug Class: **Entry and Fusion Inhibitors**

Drug Description

BMS-488043 is a novel, oral, small-molecule attachment inhibitor of HIV-1 that blocks viral entry by preventing the binding of the viral envelope protein gp120 to cellular CD4 receptors on the surface of T cells. BMS-488043 exhibits potent and selective inhibition in vitro against macrophage-, T lymphocyte-, and dual-tropic HIV-1. [1]

HIV/AIDS-Related Uses

BMS-488043, also known as 043, is an investigational entry and fusion inhibitor. In vitro susceptibility assays indicate that BMS-488043 is effective against both CCR5 and CXCR4 HIV-1 laboratory strains.[2] It was being studied in HIV infected and uninfected people.[3] [4]

Pharmacology

High rates of therapeutic failure in the HIV infected population emphasize the need for novel compounds aimed at new targets, preferably with pharmacokinetic and safety profiles superior to those of drugs currently available for the treatment of HIV infection. In particular, development of the class of antiretroviral drugs known as entry or fusion inhibitors is especially desired, because of less likelihood of developing cross resistance to other antiretroviral drugs and of better potential to work in people who have already virologically failed other regimens. Enfuvirtide is currently the only FDA- approved entry or fusion inhibitor available in the United States; all other FDA-approved antiretroviral drugs are therapeutic in nature only. The expense of enfuvirtide treatment (prohibitive to most HIV infected patients) and enfuvirtide administration via injection (because of its relatively large size) make treatment with enfuvirtide less than ideal. BMS-488043, on the other hand, is an oral, small molecule entry inhibitor that prevents the gp120 molecule of HIV from attaching to the CD4 receptor of a T cell. Because it targets the interaction between the virus and the primary CD4 receptor, BMS-488043 is effective against HIV strains utilizing either the CCR5 or CXCR4 coreceptors.[5]

In two placebo-controlled studies in HIV uninfected adults, the safety, tolerability, and pharmacokinetics of BMS-488043 capsules were evaluated. The first was an ascending single-dose study in which 6 groups of subjects (6 receiving drug, 2 placebo per group) received 200, 400, 800, 1200, 1800, or 2400 mg doses of BMS-488043. The median time to peak serum concentrations (Tmax) was 1 to 2 hours and mean peak serum concentrations (Cmax) ranged from 62 to 1,790 ng/ml for the 200 to 2400 mg groups. The area under the concentration-time curve (AUC) appeared dose related but not dose proportional for doses of 200 to 800 mg, with no significant increase in exposure observed at higher doses. A second single dose was given either as an oral solution (200 mg group), after ritonavir pretreatment (400 mg group), or after a high fat meal (800 and 1800 mg groups). Compared to capsule administration under fasted condition, solution administration resulted in threefold increased exposure to BMS-488043. Ritonavir pretreatment increased BMS-488043 exposure by 43%. Administration with food showed three- to fivefold increased BMS-488043 exposure.[6]

The second study was an ascending multiple-dose study in which four groups of subjects received 400, 800, 1200, or 1800 mg doses of BMS-488043 every 12 hours with a high fat meal. Median Tmax was 3 to 4 hours after the morning dose, and mean Cmax was 2,494 to 7,136 ng/ml. Accumulation indices (Day 14: Day 1) ranged from 1.1 to 1.6. Exposures were generally higher with a high fat meal compared to a light meal and were generally dose proportional over the dose range of 400 to 1200 mg (high fat meal) and 400 to 800 mg (light meal); exposure did not significantly increase above these doses.[7]

The antiviral activity, safety, and tolerability of BMS-488043 were evaluated in a small Phase I, placebo-controlled, ascending multiple-dose study in HIV infected adults. Participants began the study with viral loads between 5,000 and 500,000 copies/ml and CD4 counts of 250 cells/ml or greater; participants were either antiretroviral naive or had been off antiretroviral therapy for at least 16 weeks. Two groups of 15 subjects each (12

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Pharmacology (cont.)

receiving drug, 3 placebo) received 800 or 1800 mg doses of BMS-488043 or placebo every 12 hours for 8 days. Doses of BMS-488043 were administered with a high fat meal. Participants' viral load was assessed daily. Mean viral load change was about fivefold for those receiving BMS-448043; the mean maximal viral load decline from baseline during a 2-week period was tenfold. None of the placebo-treated participants had a maximal viral load decline of greater than threefold, whereas 8 of 12 of BMS-488043-treated participants had a viral load decline greater than threefold, 7 of 12 had a decline greater than tenfold, and 3 of 12 had a decline of about 31-fold.[8]

Adverse Events/Toxicity

BMS-488043 appeared generally safe and well tolerated, with no serious adverse effects or participant discontinuations observed in clinical trials enrolling HIV infected and uninfected adults.[9] [10]

Drug and Food Interactions

BMS-488043 exposure was compared in a single-dose study in HIV uninfected adults. Compared with BMS-488043 capsules under fasting conditions, oral solution administration resulted in threefold increased exposure, and administration with food showed a three- to fivefold increased exposure, suggesting that serum concentrations of BMS-488043 are higher when the drug is given in solution form or with food. Exposures were generally higher with a high fat meal compared to a light meal and were generally dose proportional over the dose range of 400 to 1200 mg (high fat meal) and 400 to 800 mg (light meal); exposure did not significantly increase above these doses. BMS-488043 exposure increased by 43% if participants had been pretreated with ritonavir.[11]

Clinical Trials

For information on clinical trials that involve BMS-488043, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: BMS-488043 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[12]

Dosage Form: BMS-488043 has been studied at doses of 200, 400, 800, 1200, 1800, and 2400 mg. Both capsule and oral solution forms have been studied.[13]

Other Names

043[14]

Further Reading

Hanna G, Lalezari J, Hellinger J, Wohl D, Masterson T, Fiske W, Kadow J, Lin P, Giordano M, Colonno R, Grasela D. Antiviral Activity, Safety, and Tolerability of a Novel, Oral Small-Molecule HIV-1 Attachment Inhibitor, BMS-488043, in HIV-1-Infected Subjects. San Francisco, Abstract 141, 2004.

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Lin PF, Ho HT, Gong YF, Dicker I, Zhou N, Fan L, McAuliffe B, Kimmel B, Nowicka-Sans B, Wang T, Kadow J, Yamanaka G, Lin Z, Meanwell N, Colonno R. Characterization of a Small Molecule HIV-1 Attachment Inhibitor BMS-488043: Virology, Resistance, and Mechanism of Action. San Francisco, Abstract 534, 2004.

Manufacturer Information

BMS-488043
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 141.

2. Bristol-Myers Squibb - Newsroom: Merck and Bristol-Myers Squibb License New AIDS Drugs to IPM for Development as Microbicides to Protect Women from HIV [Press Release], October 31, 2005. Available at: http://www.bms.com/news/press/data/fg_press_release_5975.html. Accessed 02/08/06.

3. AIDSinfonet.org - Fact Sheet 460: Attachment and Fusion Inhibitors. Available at: http://www.aidsinfonet.org/factsheet_detail.php?fsnumber=460. Accessed 02/08/06.

4. AIDSinfonyc.org - Antiretrovirals in the Pipeline. Available at: http://www.aidsinfonyc.org/tag/tx/antiretroviralsPipelineJuly05.html#intro. Accessed 02/08/06.

5. Aidsmap.com - BMS-488043. Available at: http://www.aidsmap.com. Accessed 02/14/05.

6. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 535.

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11. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 535.

12. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 535.

13. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 535.

14. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 535.